1685 #3/C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Applicant: §

J. GERSHONI §

Serial No.: 09/297,668 §

Filed: May 7, 1999 §

For: DETERMINATION AND CONTROL OF BIMOLECULAR INTERACTIONS §

Examiner: B. Forman §

Group Art Unit: 1655

Attorney Docket: 27/135

Commissioner of Patents and Trademarks

Washington, D.C. 20231

RESPONSE

Sir:

This is in response to the United States Patent and Trademark Office Action mailed Dec. 06, 2000, which response is being made on or before March 06, 2001 and for which no late fees are due. Please amend the above-identified application as follows:

AMENDMENTS

IN THE CLAIMS PLEASE AMEND CLAIMS 137-140:

137. (Twice amended) A method for preparing a conformational peptide which represents an epitope which is discontinuous in its primary amino

acid sequence [of a discontinuous epitope] of a single biological unit of an organism, the method comprising the steps of:

(a) providing a plurality of DNA fragments [corresponding to] from at least a portion of a genome of the organism by means selected from the group consisting of:

(i) synthesizing said plurality of DNA fragments [corresponding to] from said at least a portion of said genome of the organism;

(ii) digesting said at least a portion of said genome of the organism to form said plurality of fragments, said portion of said genome coding for the biological unit;

(b) ligating said plurality of fragments to form at least one ligated fragment;

(c) at least partially digesting said at least one ligated fragment to form a plurality of conformational DNA fragments for coding for the discontinuous epitope of the single biological unit, thereby forming [said] a discontinuous library;

(d) inserting said discontinuous library into an expression system; and

(e) [obtaining] preparing the conformational peptide which represents an epitope which is discontinuous in its primary amino acid sequence from said expression system.

138. (Once Amended) The method of claim 137, wherein said expression system comprises a plurality of bacteria, such that step (d) is performed by inserting each of said plurality of conformational DNA fragments of said discontinuous library into genetic material of each of said plurality of bacteria.

139. (Once Amended) The method of claim 137, wherein said expression system comprises a plurality of phages and step (d) is performed by inserting each of said plurality of conformational DNA fragments of said discontinuous library into genetic material of each of said plurality of phages.

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140. (Once Amended) The method of claim 139, wherein each of said plurality of conformational DNA fragments is cloned into a phage gene coding for a coat protein, such that the conformational peptide is displayed by said coat protein.

REMARKS

Reconsideration of the above-identified patent application in view of the amendments above and the remarks following is respectfully requested. Claims 112-143 are in this case. Claims 112-136 have been withdrawn by an election request. Claims 137-143 have been rejected under § 112, second paragraph and § 103, first paragraph. The examiner has objected to the language of claim 137 which is the independent claims in this case. Prior art of Gritz et al. and Mandeville et al. has been deemed by the examiner to render the invention of the instant application obvious.

§ 112, Second Paragraph Rejections

The applicant has amended claim 137 in accordance with the examiner's instructions as detailed hereinbelow. The examiner has objected to the use of the term "conformational peptide" in claim 137 because it is not standard scientific terminology. The applicant has responded by including a definition of the term in both the preamble and the body (e) of the claim. The added definition " a conformational peptide which represents an epitope which is discontinuous in its primary amino acid sequence [of a discontinuous epitope] " is amply supported in the specification:

> (Example 7) "A conformational peptide is a peptide which represents a discontinuous epitope, as described in the Background section above."
>
> and

(page 5, lines 5 and 6) "... an epitope is ...discontinuous in the primary amino acid sequence...". (emphasis added)

Therefore, the applicant respectfully maintains that addition of the definition requested by the examiner does not constitute an introduction of new material.

The examiner has further objected to the use of the term "corresponding" and has suggested replacing it with the term "from". The applicant has made this substitution in 137 (a) and (a(i)).

The examiner has objected to the use of the phrase "conformational fragment" in 137 (c) because of a lack of antecedent basis. The applicant respectfully suggests that the "conformational fragment" of 137 (c) is a newly formed entity which has no antecedent in other steps of the claimed method. However, the examiner's uncertainty has prompted the applicant to amend the claim to read "conformational DNA fragment". The applicant stresses that the "conformational DNA fragment" of (c) is substantially different from both the " plurality of DNA fragments" of (a) and the "ligated fragment" of (b). The difference lies in the primary amino acid sequence of the newly formed "conformational DNA fragment." Claims 138-140 have also been amended to read "conformational DNA fragment" in order to preserve antecedent basis

The examiner has objected to the use of the phrase "said discontinuous library" in 137 (c) because of a lack of antecedent basis. The applicant stipulates that, in this case, the examiner is correct and has substituted "a" for "said" in the amended claim 137 (c).

The examiner has further objected to the use of the term "obtaining" and has suggested replacing it with the term "preparing". The applicant has made this substitution in 137 (e).

The applicant respectfully suggests that claim 137, twice amended, is in condition for allowance with respect to § 112, Second Paragraph , and that claims 138-143 which depend therefrom are similarly in condition for allowance with respect to § 112, Second Paragraph.

§ 103, First Paragraph Rejections

The examiner has rejected claims 137-143 as being unpatentable over Gritz et al (hereinafter Gritz) in view of Mandeville et al. (hereinafter Mandeville).

Gritz:

Gritz teaches the production of novel genes generated by shuffling of DNA fragments. An essential feature of Gritz's teachings is the novel combination of DNA fragments derived from at least **two different yet homologous** genes. Therefore, Gritz teaches (claim 1 of Gritz) "hybrid genes" while the instant application teaches (Claim 137 instant application) "preparing a conformational peptide which represents an epitope which is **discontinuous in its primary amino acid sequence of a single biological unit** of an organism". Hence Gritz requires recombination between at least two separate biological units, while the instant application specifically precludes such a practice. Gritz clearly teaches this essential difference in the specification:

> (Column 9; lines 49-57) " Intramolecular recombination between homologous regions of the two HIV envelope genes in the parental virus will give rise to a population of progeny viruses, each of which contains **a unique hybrid envelope gene generated from the random recombination between homologous regions shared by the two original genes**. The chimeric envelope proteins encoded by these hybrid genes will contain both **novel combinations of epitopes** as well as new **discontinuous epitopes. (emphasis added)**

Thus, while Gritz uses the phrase "discontinuous epitopes", his intention is clearly different. Gritz teaches " **random recombination between ...**

the two original genes.", while the instant application teaches exclusively recombination within a single biological unit. In addition, Gritz teaches " **novel combinations of epitopes",** meaning the presence on a single peptide of epitopes having their origin in two different genes. This possibility is also excluded by the teachings of the instant application.

Because the goal of the recombination events is to form unique peptides, the examiner is asked to consider the impact of this difference at the peptide level. The example employs a given gene product Alpha having two alleles "A" and "a". The Alpha gene product is a polymer of amino acids in which each amino acid has a distinct position. The Alpha gene codes for a polypeptide in which the amino acids correspondingly each have a single and distinct position in the polypeptide chain. Schematically one can view the two peptides encoded by the two alleles as:

A	B	C	D	E	F	G	H	I	J	K	AA seq. "A"
a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	AA seq. "a"
1	2	3	4	5	6	7	8	9	10	11	position

According to the teachings of Gritz , "a unique hybrid gene generated from the random recombination between homologous regions shared by the two original genes" will be formed. Such a hybrid will have the form of, for example:

A	B	**c**	**d**	E	F	**g**	**h**	I	J	K	A/a recomb. 1
A	B	**c**	**d**	E	F	G	H	I	J	K	A/a recomb. 2
A	B	C	D	E	F	**g**	**h**	I	J	K	A/a recomb. 3
1	2	3	4	5	6	7	8	9	10	11	position

However, in all of these examples at positions 3 and 4, C and D have been exchanged for **c** and **d**, and G and H are exchanged for **g** and **h** at positions 7 and 8. In no case does any amino acid appear in a new position. Therefore when Gritz teaches a discontinuous epitope, the teaching is of, for example, positions 2-3; 4-5; 6-7; or 8-9 or sequences containing those

positions (underlined) which contain amino acids encoded by two separate alleles. According to Gritz, the positions of all residues are not altered and in fact must not be altered in order to ensure the potential functionality of the products after combinatorial shuffling.

In stark contrast to those teachings, the instant application requires recombination within a single biological unit. Use of a second gene variant is strictly precluded and the shuffling is not concerned with allelic variations. Teachings of the instant application therefore produce recombinants of the type:

D	E	F	G	A	B	C	H	I	J	K	
c	**a**	**b**	**d**	**e**	**f**	**g**	**i**	**j**	**k**	**h**	"A" recomb.
c	**a**	**b**	**d**	**e**	**f**	**g**	**i**	**j**	**k**	**h**	"a" recomb.
1	2	3	4	5	6	7	8	9	10	11	position

In the "A" recombinant discontinuity occurs at positions 4-5 and 7-8. In the "a" recombinant discontinuity occurs at positions 1-2; 3-4; 7-8 and 10-11. Therefore any sequence containing these positions has the potential to define a discontinuous epitope. The type of recombination events taught by Gritz can not produce this type of discontinuous epitope because the teachings of Gritz strictly require maintaining relative positions of the residues. At the same time, teachings of the instant application strictly require shuffling segments within a linear sequence to generate novel positional combinations without substituting amino acids sources outside the original biological unit.

The applicant stipulates that the undefined phrase "discontinuous epitope" was a potential source of confusion and thanks the examiner for suggesting to define the phrase within the claim. The applicant respectfully suggests that claim 137 twice amended, which includes the definition " a conformational peptide which represents an epitope which is discontinuous in

its primary amino acid sequence of a single biological unit of an organism" will serve to eliminate this confusion.

Mandeville:

Mandeville teaches a set of combinatorial libraries which are phage displayed. The purpose is to create a large collection of totally random peptide structures. This is clearly taught in the Mandeville specification:

(Col. 8; lines 58-61) "A collection of oligonucleotides encoding all possible decapeptides was synthesized with a self complementary 3' terminus...".

No design or preconception or relationship to the original ligand or binding site is required, or even allowed, by these teachings. Mandeville's teachings rely solely on the idea that by generating enormous collections of truly random peptides one can screen for a single clone of the library that can mimic a desired functional binding site. This clone then becomes the peptidomimetic. Mandeville proceeds to suggest that the first selected mimetic can in turn be used to screen a second (or the first) library to select yet an additional mimetic that would functionally resemble the original ligand used to screen the first library. These teachings resemble the concept that an anti-idiotypic antibody could elicit an immune response similar to that caused by the original antigen. Mandeville argues that a defined set of potential libraries provide a vast collection of random peptides, from which functional mimetics that have no requirement to be structurally similar in any way to the original binding site or ligand may be selected by chance.

In the instant application there is a strict requirement for a similarity between the ultimate novel product and the original binding site. In contrast to the teachings of Mandeville, the teachings of the instant application

require beginning from a very limited and defined set of peptides. The peptides are defined by the nucleotide sequences from which they are derived. Specifically, those nucleotide sequences must be (claim 137 twice amended) either (i) a synthesized plurality of DNA fragments which are identical to at least a portion of the genome of an organism or (ii) a plurality of DNA fragments created by digesting at least a portion of the genome of the organism to form a plurality of fragments. In either case, the total number of clones to be screened, even after the subsequent ligation and re-digestion steps taught in the instant application, is far lower than the number required according to the teachings of Mandeville. As a result, the teachings of the instant application insure a higher success rate during subsequent screening. This is because, in contrast to prior art teachings, completely random peptides are not generated. Instead, peptides which have elements of the original AA sequence, in a random arrangement, are generated. Thus, the generated conformational peptides of the instant application are highly suited to a specific purpose, in contrast to the random peptides of Mandeville (and others) which have similar applicability to all problems without any focus on a specific problem. In short, the instant application teaches creating a unique library of conformational DNA fragments, and then of conformational peptides, for each biological unit. There is neither a hint nor a suggestion of this idea in the teachings of Mandeville. Alternately or additionally the teachings of the present invention allow analysis of biological units too complex to be analyzed using the "random peptide" approach of Mandeville.

In summary, Gritz contains neither a hint nor a suggestion that recombination of non-homologous sequences within a single sequence is feasible. Mandeville contains neither a hint nor a suggestion that discontinuous amino acid binding sites may be generated in a non-random fashion. Therefore the teachings of the present invention are not obvious with respect to Gritz in view of Mandeville. The examiner's objection based upon § 103, First Paragraph is traversed.

The applicant respectfully suggests that claim 137 twice amended is now in condition for allowance and that amended claims 138-40 and claims 141-143, which depend therefrom are also in condition for allowance. Therefore allowance of claims 137-143 is respectfully requested.

Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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